Acyloxylation of Methylbenzenes by Potassium Peroxydisulphate

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Potassium peroxydisulphate in acetic acid containing 9% trifluoroacetic acid has been shown to oxidize a number of substituted methylbenzenes, yielding nuclear and side-chain acetates. In the presence of copper(II) acetate nuclear substitution is suppressed, and a mixture of side-chain acetate and trifluoroacetates is obtained. This mixture can be hydrolysed to the corresponding benzyl alcohol in total yields varying from 18 to 66%. The mechanism has been investigated and the results obtained support a radical cation pathway.

WE have previously explored the use of potassium peroxydisulphate as an oxidant for a variety of substituted benzenes in the presence of catalytic amounts of silver(I) [1] or palladium(II) [2] complexes in acetic acid. Other workers have found the same reagent to effect the hydroxylation of benzenes [3,4] and the oxidation of substituted alkylbenzenes to the corresponding carboxy derivatives.[5,6] Mechanistic investigations have shown that the sulphate anion radical can oxidize anisole to its radical cation.[7,8]

Oxidations have also been performed in the presence of chloride ion.[9] In this case, however, the reaction did not proceed *via* radical cations but was shown to involve electrophilic substitution by molecular chlorine.[9]

In our previous work [1,2] on the peroxydisulphate oxidation of aromatic compounds in the presence of either silver(II) or palladium(II) no oxidation of the aromatic substrate occurred in control experiments in the absence of the metal ion. Since these reactions were run with acetate ion present and acetate is known to be very rapidly oxidized by sulphate anion radical [12] we suspected that the inconsistency between our results [1,2] and those referred to above [7,8] might be due to competition from this process. We therefore chose trifluoroacetic acid (TFA) as a co-solvent for the reaction between sulphate anion radical and aromatic compounds in acetic acid, thus suppressing [OAc] to very low levels, and have indeed been able to acetoxylate a series of compounds by this simple procedure.

RESULTS

The presence of 9% TFA in acetic acid increases the selectivity for oxidation of the aromatic compound remarkably. In the presence of catalytic amounts of copper(II) ions methylbenzenes are oxidized to a mixture of esters according to reaction (1), which can be converted into the corresponding benzyl alcohols.

$$\mathrm{ArCH_3} \xrightarrow[\mathrm{Cu(OAc)_2}]{\mathrm{K_2S_2O_8}} \mathrm{ArCH_2OCOCH_3} + \mathrm{ArCH_2OCOCF_3} \xrightarrow{\mathrm{H_2O}} \mathrm{ArCH_2OH} \quad (1)$$

Reaction of mesitylene by potassium peroxydisulphate in acetic acid containing 9% TFA at 110 °C for 4 h resulted in the formation of a mixture of 2,4,6-trimethylphenyl acetate and 3,5-dimethylbenzyl acetate in a low yield (15%, see Table 1). Control experiments showed that no reaction occurred in the absence of potassium peroxydisulphate and/or TFA. When TFA was substituted by other strong acids, such as sulphuric or methanesulphonic acid, no identifiable products were detected. The influence of different metal ions on this reaction was also investigated. It is known that silver(I) promotes the decomposition of peroxydisulphate ion according to reaction (2).[13] The

$$\mathrm{Ag^+ + S_2O_8{}^{2-} \longrightarrow Ag^{2+} + SO_4{}^{2-} + SO_4{}^{-\cdot}} \quad (2)$$

sulphate radical anion formed in this way could then act as an oxidant towards the aromatic species. In this case, however, no effect was observed when the reaction was run in the presence of silver(I) acetate.

Iron(II) also promotes the decomposition of peroxydisulphate ion to the sulphate anion radical in aqueous solution.[4] Addition of a small amount of iron powder (iron reacts easily with hot acetic acid) caused no significant change in the product distribution. Copper(II) is known to oxidize benzyl radicals to benzyl cations rapidly.[14] If the low yield in experiment 1 (Table 1) was due to radical-induced side-reactions, this might then be inhibited by copper(II). In a typical experiment, a mixture of mesitylene, copper(II) acetate, potassium peroxydisulphate ($\mathrm{Cu^{II}}$–$\mathrm{K_2S_2O_8}$ 1 : 10), and acetic anhydride in acetic acid–TFA was stirred at 110 °C for 4 h. In this case, the yield of product increased considerably (see Table 1, experiment 3). Also, the amount of nuclear acetate formed decreased and a new product, identified as 3,5-dimethylbenzyl trifluoroacetate, appeared. Due to the instability of this ester the reaction was analysed after hydrolysis to the corresponding benzyl alcohol.

TABLE 1

Acyloxylation of mesitylene in acetic acid–TFA (10 : 1) with different reagents [a]

		Acyloxy products			
		Isomer distribution			
Experiment	Additive (mmol)	α	Nuclear	Yield [e] (%)	Dimers
1 [b]		33	67	15	Trace
2	NaOAc (10)			0	
3 [c]	$\mathrm{Cu(OAc)_2}$ (1)	92 [d]	8	45	Trace
4	$\mathrm{Cu(OAc)_2}$ (10) [f]			0	
5	AgOAc (1)	34	66	16	
6	Fe (1)	33	67	14	

[a] Reaction conditions, unless otherwise noted: mesitylene (10 mmol), $\mathrm{K_2S_2O_8}$ (10 mmol), acetic anhydride (2 ml), TFA (5 ml), glacial acetic acid (50 ml), 110 °C, 4 h reaction period. [b] Without $\mathrm{K_2S_2O_8}$ no acetoxy compounds were formed. Without TFA 3,5-dimethylbenzaldehyde and a small amount of acetoxy compounds were formed. [c] Without TFA only trace amounts of acetoxy compounds and dimers were found. With $\mathrm{Cu(OAc)_2}$ present both benzyl trifluoroacetate and acetate were formed. If TFA was replaced by $\mathrm{MeSO_3H}$ or $\mathrm{H_2SO_4}$ trace amounts of acetoxy compounds were formed. [d] Analysed as 3,5-dimethylbenzyl alcohol. [e] G.l.c. yield based on initial amount of substrate. [f] Without potassium peroxydisulphate.

Reaction of toluene with potassium peroxydisulphate in acetic acid–TFA gave a mixture of bibenzyl and benzyl acetate in low yield. In the presence of copper(II) acetate no bibenzyl was formed, and the reaction course was diverted to give moderate yields of benzyl trifluoroacetate. The results from these experiments are summarized in Table 2 (experiment 7).

TABLE 2

Side-chain acyloxylation of some methylbenzenes by potassium peroxydisulphate with copper(II) acetate as catalyst [a]

Experiment	Compound	Yield of side-chain acyloxy products (%) for different reaction periods [b] 2 h	6 h	10 h
7	Toluene [c]	20	33	41
8	*o*-Chlorotoluene	9	20	
9	*m*-Chlorotoluene	7	18	
10	*p*-Chlorotoluene	17	47	
11	*p*-Bromotoluene	26	36	51
12	*p*-Fluorotoluene	12	25	28
13	*o*-Xylene	11	35	61
14	*m*-Xylene	10	32	60
15	*p*-Xylene [d]	20	50	54
16	*p*-t-Butyltoluene	27	56	66

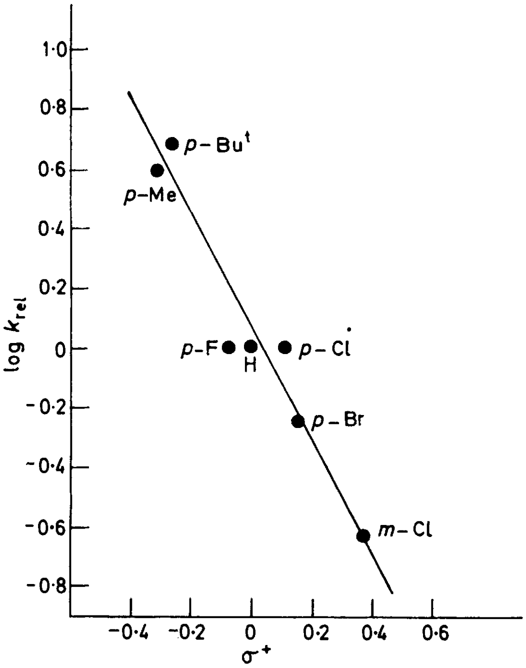
[a] Reaction conditions: aromatic compound (10 mmol), $K_2S_2O_8$ (10 mmol), $Cu(OAc)_2$ (1 mmol), acetic anhydride (2 ml), TFA (5 ml), glacial acetic acid (50 ml), 110 °C. [b] Analysed as benzyl alcohols. G.l.c. yield based on initial amount of substrate. In some cases traces of nuclear substitution products were formed. [c] Without $Cu(OAc)_2$ the products consisted of 25% benzyl acetate and 75% bibenzyl. Trace amounts of nuclear acetates were also formed. [d] Without $Cu(OAc)_2$: nuclear acetate 10%, side-chain acetate 90%.

A number of substituted toluenes has been oxidized using the potassium peroxydisulphate–copper(II) acetate system in acetic acid–TFA in order to investigate the synthetic scope of the reaction. As an example, oxidation of hexamethylbenzene yields pentamethylbenzyl alcohol in 38% yield after a 3 h reaction period at 110 °C followed by hydrolysis. Additional results are shown in Table 2, experiments 7—16. Oxidation of strongly deactivated substrates was not successful. Thus, *p*-nitrotoluene did not react under these conditions, and *p*-methylacetophenone gave only a very small amount of an acetate.

It has previously been shown that the anodic acetoxylation of anisole, deuteriated in the ring,[15] or trifluoroacetoxylation of deuteriated benzene by cobalt(III) trifluoroacetate occur with the same rates as with the protiated compounds.[16] [2,4,6-^{2}H]Mesitylene was employed to study the isotope effect for nuclear substitution with potassium peroxydisulphate in acetic acid–TFA (in the absence of any metal ion). A comparison between nuclear and α-substitution in deuteriated and protiated mesitylene showed no primary kinetic isotope effect (k_H/k_D 1.0 ± 0.2). Using the same oxidant in the presence of copper(II) acetate we studied the oxidation of a mixture of equal amounts of toluene and perdeuteriotoluene. By determining the deuterium content of the side-chain substituted products a k_H/k_D value of 2.2 ± 0.2 (2.3 ± 0.2 for benzyl trifluoroacetate and 2.1 ± 0.2 for benzyl acetate) was calculated.

To determine whether proton exchange between solvent and substrate occurred during the reaction, toluene was oxidized by potassium peroxydisulphate in [1-^{2}H]acetic acid–[1-^{2}H]TFA. After isolation of the remaining starting material and products the deuterium content was determined by n.m.r. This was < 10% for starting material, benzyl acetate, and bibenzyl. Nor in the presence of copper(II) acetate was any deuterium exchange observed.

The relative rates of oxidation of substituted toluenes were determined by heating an equimolar amount of the substituted toluene and toluene itself in acetic acid–TFA to 110 °C in the presence of potassium peroxydisulphate and copper(II) acetate (10 : 1). A tenfold molar excess of aromatic compound was used. After 1 h the ratio of the benzyl alcohols was determined by g.l.c. after hydrolysis of the formed esters. The results are shown in the Figure as a Hammett plot of log k_{rel} *versus* σ^+, yielding a ρ value of −1.9 (*r* 0.97). This value may be compared with a ρ value of −2.4 obtained in cobalt(III) acetate oxidation of substituted toluenes,[10] and a ρ value of −2.5 from the reaction of $SO_4^{-\bullet}$ with substituted benzenes in aqueous solution.[17]



Relative reactivities of substituted toluenes toward potassium peroxydisulphate–copper(II) acetate in acetic acid–TFA at 110 °C

Oxidation of substrates in which no side-chain was available for substitution, such as anisole, naphthalene, benzene, or chlorobenzene, gave no nuclear substitution products, neither in the presence of copper(II) acetate nor in its absence.

DISCUSSION

Looking at the results from the oxidation of toluene with potassium peroxydisulphate alone, the formation of bibenzyl shows the intermediacy of the benzyl radical. This intermediate can be formed *via* two pathways, either a direct hydrogen atom abstraction by the sulphate anion radical or an electron transfer from the arene to the sulphate anion radical as shown in reactions (3) and (4), respectively. The benzyl radical would then either

$$ArCH_3 \xrightarrow{SO_4^{-\bullet}} ArCH_2^{\bullet} \qquad (3)$$

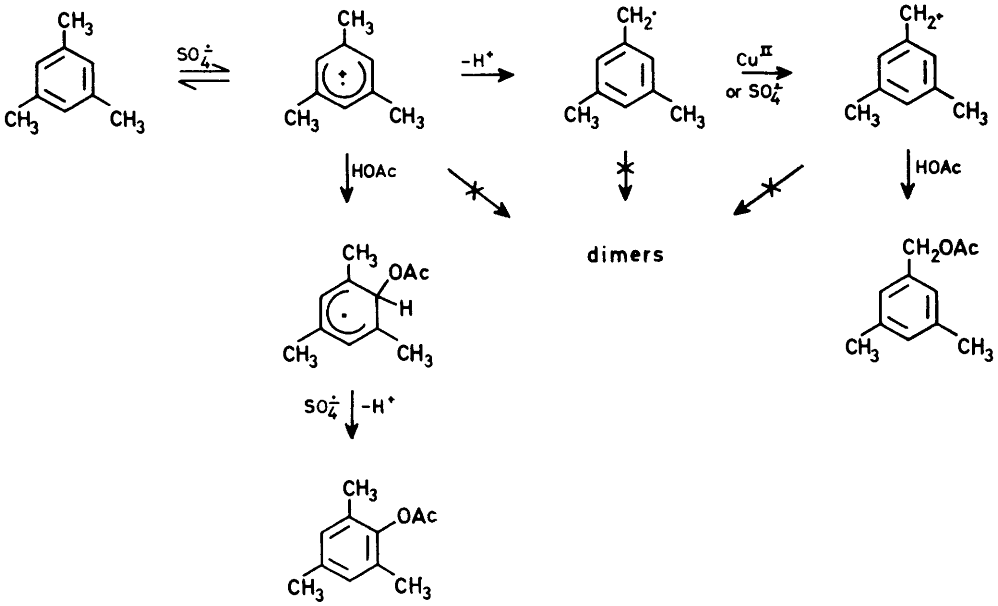
$$ArCH_3 \xrightarrow{SO_4^{-\bullet}} ArCH_3^{+\bullet} \xrightarrow{-H^+} ArCH_2^{\bullet} \qquad (4)$$

dimerize to bibenzyl or undergo oxidation to give benzyl cation which would be captured by acetate ion or acetic acid to give benzyl acetate. The formation of the nuclear acetate from mesitylene supports the radical cation mechanism (4). To form a nuclear acetate *via* reaction (3) there must be a fast equilibrium between the benzyl radical and the corresponding radical cation.

$$\mathrm{ArCH_3^{+\cdot}} \underset{\mathrm{H^+}}{\overset{\mathrm{-H^+}}{\rightleftharpoons}} \mathrm{ArCH_2^{\cdot}} \qquad (5)$$

However, in deuteriated acetic acid–TFA no deuterium exchange is observed, which rules out this equilibrium as an explanation for the formation of nuclear acetates.

The intermediacy of a benzyl radical is also in accord with the effect of copper(II) on the oxidation of toluene. In this case, rapid oxidation [18] of the benzyl radical by copper(II) to the benzyl cation would compete with radical coupling. Another significant effect of copper(II) is the change in the nuclear to side-chain acetate ratio (N : S ratio) in the oxidation of mesitylene from 2.0 without copper(II) to 0.087 in its presence. This observation is in agreement with the hypothesis that copper(II) catalyses the transformation of the radical cation to the benzyl cation. The N : S ratio obtained in the absence of copper(II) is nearly the same as the N : S ratio of 1.7 observed in the oxidation of mesitylene by silver(II) in acetic acid [19] and an N : S ratio of 3.6 for the anodic acetoxylation of the same substrate,[20] which have both been shown to involve radical cations.



SCHEME

In the light of these results, we propose the mechanism in the Scheme for the oxidation of substituted toluenes by potassium peroxydisulphate in acetic acid containing TFA, using mesitylene as an example.

The electron transfer pathway is also supported by the relative reactivity of substituted toluenes toward potassium peroxydisulphate–copper(II) acetate which follows a linear Hammett relationship. A good correlation with σ^+ [21] yielded a ρ value of -1.9 (Figure). This value indicates considerable charge development on the arene in the transition state and is not consistent with a free-radical mechanism. [As an example, hydrogen atom abstraction from substituted toluenes by manganese(III) acetate in acetic acid gave a ρ value of -0.63.[22]]

The observed isotope effect (k_H/k_D 2.2) for side-chain substitution is in accord with a rate-limiting proton loss from the benzylic position. This value may be compared to those obtained in the anodic side-chain acetoxylation [11] (k_H/k_D 2.6), the silver(II) acetoxylation [1] (k_H/k_D 5.9), and the $\mathrm{Mn^{III}}$ acetoxylation [23] of *p*-methoxytoluene (k_H/k_D 5.1).

TFA plays an important role for the oxidative power of peroxydisulphate in acetic acid. We associate this increased reactivity to at least three factors. First, this strong acid probably protonates the persulphate ion, and the protonated species would be thermally less stable than the peroxydisulphate ion. Secondly, as noted in the Introduction, the presence of TFA should suppress the concentration of acetate ion, which is known to undergo very fast oxidative decarboxylation by sulphate anion radical.[18] Thirdly, it is known that strong acids stabilize aromatic cation radicals to such an extent that even e.s.r. measurements have been made possible for a number of radical cations which were too unstable to be observed in other solvents.[10,24]

EXPERIMENTAL

Materials.—All chemicals used in this investigation were either purchased in the highest quality available or prepared according to known procedures. [2,4,6-^{2}H]Mesitylene was obtained by equilibrating mesitylene three times with a mixture of deuterium oxide and deuteriated sulphuric acid. The substituted benzyl alcohols were prepared by anodic oxidation of substituted toluenes.[25]

Acyloxylation Procedure.—A mixture of substrate, potassium peroxydisulphate, copper(II) acetate, acetic anhydride, and trifluoroacetic acid (or other strong acids) in glacial acetic acid (or [1-^{2}H]acetic acid) was stirred vigorously for different periods at 110 °C. The mixture was worked up by the addition of saturated sodium hydrogencarbonate solution and ether extraction. After evaporation the residue was hydrolysed by ethanolic potassium hydroxide followed by ether extraction. The competition experiments were carried out in the following way: toluene (10 mmol) and the substituted toluene (10 mmol) were heated at 110 °C in a solution of glacial acetic acid (50 ml), TFA (5 ml), and acetic anhydride (2 ml) with potassium peroxydisulphate (1 mmol) and copper(II) acetate (0.1 mmol) during 1 h. The work-up procedure was the same as above.

Isotope Exchange Experiment.—Toluene (50 mmol) in [1-^{2}H]acetic acid (200 ml) and [1-^{2}H]trifluoroacetic acid (50 ml) was stirred with potassium peroxydisulphate (50 mmol) at 110 °C for 4 h. After addition of dichloromethane and washing with water and saturated sodium hydrogencarbonate, toluene was distilled off (24.4 mmol). The residue was subjected to column chromatography on silica gel. Bibenzyl (5.7 mmol) was eluted with tetrachloromethane. To isolate benzyl acetate (2.5 mmol), a mixture of tetrachloromethane and chloroform (3 : 1) was used. The deuterium content was determined by n.m.r. on both starting material and products.

Analysis.—Yields and isomer distributions were determined using a Varian 1400 gas chromatograph, equipped with an electronic integrator (Hewlett-Packard 3380 A) on a (2 m × 3 mm) 5% NPGS on Chromosorb W column. The yields were determined using benzyl alcohol as an internal standard (in experiment 7, *p*-chlorobenzyl alcohol) calibrated against authentic samples. N.m.r. spectra were recorded on a Varian A 60 spectrometer and m.s. analysis was performed with the LKB 9000 instrument.

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